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In cats with cardiogenic thromboembolism, is treating with aspirin associated with a better outcome?

Clinical scenario

You are presented with a mature feline patient with a peracute onset of tachypnoea and non-ambulatory, paraparesis. The cat is hypothermic, with a sternal systolic murmur and cold, stiff hindlimbs with pale cyanotic nail beds and poorly palpable hindlimb pulses. You provide oxygen therapy, diuretics and analgesia and perform a cardiac ultrasound which identifies ventricular myocardial thickening and left atrial enlargement, consistent with hypertrophic cardiomyopathy (HCM). You diagnose the cat with a cardiogenic Feline Arterial Thrombo-Embolic (FATE). Your clients are keen to explore treatment for the patient and as part of this, you plan to instigate antiplatelet therapy to reduce the likelihood of a second event - there is no licensed antiplatelet therapy for cats, and a colleague has always used aspirin however you are uncertain if there is any evidence to support its use: what does the literature say?

The question

In [cats with cardiogenic thromboembolism], is treating with [aspirin] associated with a better outcome [reduced risk of arterial thromboembolism or death] compared with [alternative treatments, no treatment or placebo]?

Search parameters & databases searched

Databases searched, dates covered, and terms used:

CAB Abstracts on OVID (1973-2019 Week 2):

(cats/ or (cats or cat or feline* or felis).mp) AND (cardiomyopathy/ or (hcm or "hypertrophic cardiomyopathy" or "hypertrophic cardiomyopathies" or cardio* or cardia*).mp) AND (aspirin/ or salicylic acids/ or (aspirin or "salicylic acid" or "sodium salicylate").mp)

Medline on OVID (1946-2019 Week 2):

(Cats/ or (cats or cat or feline* or felis).mp) AND (Cardiomyopathy, Hypertrophic/ or (hcm or "hypertrophic cardiomyopathy" or "hypertrophic cardiomyopathies" or cardio* or cardia*).mp) AND (aspirin/ or salicylic acid/ or sodium salicylate/ or (aspirin or "salicylic acid" or "sodium salicylate").mp)

Search results

Database	Number of results	Excluded – inadequately related to PICO	Excluded – In vitro/not in cats	Excluded – Non-systematic reviews (opinion articles etc.)	Total relevant papers
CAB Abstracts	28	10	3	12	3
MedLine	48	25	13	7	3
Total relevant papers when duplicates removed: 3					

Search last performed: 11/01/2019

SUMMARY OF EVIDENCE

Paper 1: Smith, S. *et al.* (2003): Arterial Thromboembolism in Cats: Acute Crisis in 127 Cases (1992–2001) and Long-Term Management with Low-Dose Aspirin in 24 Cases.

Patient group: 44 cats who were discharged following presentation (of the 127 cats who presented overall) with arterial thromboembolism at a University Teaching Hospital in North America between 1992-2001. 18 were treated with high dose aspirin (HDA: $\geq 40\text{mg}/\text{cat}$ PO q24-72h), 24 with low-dose aspirin (LDA: $5\text{mg}/\text{cat}$ PO q72h) and 2 without anticoagulants.

Study type: Retrospective cross-sectional study.

Outcomes: Primary measured endpoints relevant to this clinical scenario were recurrence of FATE and death in the cohort who survived to discharge. Other outcomes for which data was collected included frequency of side effects attributed to aspirin treatment.

Key results: There was no significant difference in survival curves between cats receiving HDA and LDA ($P = 0.882$). Aspirin-attributed side effects were apparently more frequent for HDA-treated cats (gastrointestinal signs occurred in 22% of HDA versus 4% of LDA cats: a significant difference was not proven).

Other results in this patient group included that cats presenting with congestive heart failure (CHF) at the time of ATE had significantly shorter long-term survival after discharge than cats without (77 vs. 223 days, $P = 0.016$), 25% of cats experienced a secondary FATE (191 ± 152 days), and median survival time was 117 days.

Of the 127 cats presenting with FATE (regardless of survival to discharge), 67% were male (odds ratio 1.75, $P = 0.003$) and those with an underlying cardiac cause identified were 83% male. 4% of cats found to have concurrent cardiovascular disease at the time of their embolism had no audible auscultatory cardiac abnormality.

Study weaknesses: The number of controls discharged without aspirin treatment was very small, so difference in survival or FATE recurrence between aspirin-treated and non-treated groups was not statistically analysed (or results not reported). There was variability between concurrent medication administration prior to, and following discharge from, the presenting FATE episode, including six cats who were treated with aspirin prior to their first episode (3 HDA, 3 LDA) and two cats who received heparin as well as aspirin after discharge from hospital post-FATE which may affect their results. The rationale for why each cat was assigned each dose is not clear and is likely to have been affected by clinical bias at the time of prescription due to the non-randomised retrospective non-blinded nature of this data. Whether or not a significant difference was found between FATE recurrence in LDA and HDA groups was not reported (although it appeared cats treated with LDA had better survival of a subsequent ATE than cats treated with HDA).

Paper 2: Borgeat, K. *et al.* (2013): Arterial Thromboembolism in 250 Cats in General Practice: 2004-2012.

Patient group: 97 cats in whom treatment had been attempted for FATE (from a cohort of 250 cats presenting for FATE, the rest having been euthanised at presentation) managed by 3 general practices in the United Kingdom. 25 cats received aspirin, 10 received aspirin and clopidogrel, 2 cats received clopidogrel alone.

Study type: Retrospective cross-sectional study.

Outcomes: Mortality (spontaneous death or euthanasia) <1 day, 1-7 days and ≥ 7 days; circumstances of death (confirmed or suspected ATE-related, relating to dyspnoea, or neither ATE- nor dyspnoea-related).

Key results: Absence of antiplatelet therapy (aspirin, clopidogrel or both) was a negative predictor of <7 -day mortality (hazard ratio 8.26, confidence interval 1.39-50, $P = 0.001$): this was not correlated to survival beyond 7 days post-presentation. Other results of the study included that lower rectal temperature was an independent predictor of mortality <1 day (36 versus 27.8°C ; hazard ratio 1.44; 95% confidence interval, 1.002 - 2.071; $P < 0.001$) and <7 days (36.8 versus 38.6°C ; hazard ratio 2.25; 95% confidence interval, 1.12-4.48; $P = 0.021$). Presentation to the practice within normal hours (data available for 2 of the 3 practices only, $P = 0.03$), only a single leg affected (rather than multiple legs, $P = 0.001$) and absence of CHF at presentation ($P < 0.001$) were all significantly associated

KNOWLEDGE SUMMARY

with survival for more than 24 hours. Only a single leg being affected ($P = 0.001$), being non-dyspnoeic at presentation ($P = 0.045$), no CHF ($P = 0.02$) and not being treated with heparin ($P = 0.023$) were all indicators of survival 1-7 days post-presentation. Males were not noted to be significantly overrepresented (57.4%) in this study.

Study weaknesses: Due to the retrospective nature of this study, some records are incomplete and lacking information relevant to their investigation, for example: only 63 of the 97 cats who underwent treatment for their thromboemboli had sufficient history to identify the presence or absence of CHF at presentation (42 were in CHF), and as 52/97 had echocardiographically proven cardiac disease it is not clear how many of the cats had underlying cardiac disease. They do not note whether any of the 29/250 cats with previously-diagnosed cardiomyopathy in the original cohort were on medication to manage their condition prior to their first thromboembolism. The authors identify that the protective value of antiplatelet therapy between 1-7 days post-thrombus may be spurious, and no prolonged benefit was recorded after 7 days. Additionally, the aspirin dosage used was not reported. As with Smith et al. (2003), the fact that this is a retrospective study means that the prescription of the antiplatelet drugs in each case is likely to have been affected by some level of clinical bias, and roughly half of the cats surviving >24 hours also received heparin which may have affected the results.

Paper 3: Hogan, D. *et al.* (2015): Secondary prevention of cardiogenic arterial thromboembolism in the cat: the double-blind, randomized, positive-controlled feline arterial thromboembolism; clopidogrel vs. aspirin trial (FAT CAT).

Patient group: 75 cats with underlying cardiac disease (not in unstable CHF) who had survived a FATE in the 1-3 months before enrolment in the study, under the care of 52 practices throughout North America, New Zealand and Europe. 39 cats (52%) were treated with clopidogrel (18.75 mg/cat PO q24h), and 36 (48%) with aspirin (81 mg/cat PO q72h).

Study type: Multicenter, double-blind, randomized, positive-controlled study.

Outcomes: The primary outcome measured was recurrence of FATE. The secondary endpoint was death (natural or sudden death, or euthanasia for any reason). A combined endpoint of recurrence and cardiac-associated death (or euthanasia) was also evaluated. Other relevant outcomes included whether aspirin or clopidogrel administration was associated with any adverse reactions.

Key results: Compared with aspirin, clopidogrel administration significantly reduced the likelihood of recurrent ATE (75% versus 49%; $P = 0.024$) and prolonged median time to secondary ATE (192 days (95% confidence interval 62-364) versus 443 days (95% confidence interval 195-990) respectively). Clopidogrel administration significantly reduced the likelihood of the combined endpoint of secondary ATE and/or cardiac-associated death ($P = 0.033$) and increased median time to the combined endpoint (346 days for clopidogrel (95% confidence interval 146-495 days) versus 128 days (95% confidence interval 58-243 days) for aspirin). Both drugs were well tolerated - one cat in each group experienced adverse effects. Significant-but-clinically-relevant changes to biochemical and haematological parameters studied were not found between treatment groups. The results also showed uniformity with Smith et al. (2003) in finding a strong male gender bias (76% of cats, $P < 0.001$). 15% of cats had previously been diagnosed with cardiac disease prior to their first thromboembolism, similar to the 11.6% identified in Borgeat al. (2014)'s study but differing from Smith et al. (2013) who found only 7% to have a prior diagnosis.

Study weaknesses: The primary weakness of this study is the absence of a negative control group, so although clopidogrel appears superior to aspirin, we cannot deduce with certainty whether there is an overall benefit of clopidogrel compared with a lack of treatment or placebo. Other weaknesses of the study include that 2 cats had received aspirin (one assigned to each group) and one clopidogrel (assigned to the aspirin group) prior to the trial period and that 2 cats from each of these groups were lost to follow-up: given the limited sample sizes these points may or may not be of significance. In comparison with the two other papers discussed here, however, *all* patients in the studied population had underlying cardiac disease proven by echocardiography or review of images by a cardiologist.

Comments

Many of the papers found through database searching were non-systematic review (opinion) articles. Whilst many of the total resultant papers did discuss or mention the use of aspirin in the prevention of thromboembolism, they did not directly investigate the effectiveness of it nor compare it with alternatives and therefore had to be excluded. Difficulties in appraising the evidence included comparison of aspirin in combination with another treatment to no treatment, or a lack of control when comparing aspirin alone to another treatment or another dose. Doses of aspirin used in all studies varied and none were identical to any of the BSAVA dose recommendations.

The strength of evidence is markedly strongest for Hogan et al. (2015) due to it being a prospective, double-blinded, randomised, more markedly multicenter clinical trial, and having increased their cohort size following repeat power calculations. Of the retrospective papers, Borgeat et al (2013) was strongest, being a multicenter study with a larger patient population than Smith et al (2003).

Frequency of side-effects (gastrointestinal signs) with aspirin appear to be low (especially with conservative doses of less than 40mg/cat q24-72hrs, although 81mg/cat q72hrs was well tolerated by the cats in Hogan et al. (2015)), however the overall weight of evidence in favour of prescribing aspirin is poor, and there is strong evidence that clopidogrel is a superior antiplatelet choice. Given the increased frequency of side effects in HDA-treated cats (Smith et al. 2003), conservative aspirin dosing (such as the 'low dose' detailed in the BSAVA formulary: 18.75mg/cat three times weekly) may be prudent if prescribed at all.

Clinical bottom line

Based upon current evidence, aspirin appears to be well-tolerated, particularly at lower doses, however there is no evidence that aspirin is effective in preventing recurrent cardiogenic thromboembolism or cardiac-associated death in cats with cardiac disease. Aspirin appears to be inferior to clopidogrel for the prevention of subsequent thromboembolic events and in promoting survival in cats with a history of ATE.

Authors of this Critically Appraised Topic

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